**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

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| **IN RE:**<br>**BRIMONIDINE PATENT LITIGATION** | **C.A. No. 07-md-01866 GMS** |

# THE EXELA DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF

**RICHARDS, LAYTON & FINGER, P.A.**

Frederick L. Cottrell III
Kelly E. Farnan
One Rodney Square
920 North King Street
P.O. Box 551
Wilmington, Delaware 19801
Tel.: (302) 651-7700
Fax: (302) 651-7701
cottrell@rlf.com
farnan@rlf.com

**FROMMER LAWRENCE & HAUG LLP**

Daniel G. Brown
Arthur L. Hoag
Barry S. White
David A. Zwally
Omar Jabri
745 Fifth Avenue
New York, New York 10151
Tel.: (212) 588-0800
Fax: (212) 588-0500
dbrown@flhlaw.com
ahoag@flhlaw.com
bwhite@flhlaw.com
dzwally@flhlaw.com
ojabri@flhlaw.com

*Attorneys For Defendants*
*Exela Pharmsci, Inc.*
*Exela Pharm Sci, Pvt. Ltd.,*
*Paddock Laboratories, Inc.,*
*and PharmaForce, Inc.*

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## I. INTRODUCTION

This MDL proceeding involves two different patent infringement actions filed by Allergan, Inc. ("Allergan"). In the first action, Allergan has now notified the Exela Defendants[1] it is asserting only sixteen claims of U.S. Patent No. 6,641,834 ("the '834 patent") based on Exela's Abbreviated New Drug Application ("ANDA") No. 78-590. In the second action, Allergan is asserting a total of five patents (the '834 patent and four other patents) against Apotex, Inc. and Apotex Corp based on a different ANDA. The Exela Defendants in this *Markman* brief will address only the claims of the '834 patent that are asserted against them.[2]

The '834 patent claims a therapeutically effective ophthalmic composition having up to about 0.15% (w/v) of the pharmaceutical compound brimonidine tartrate (or other salts), formulated at a pH of 7.0 or greater, wherein the active ingredient is soluble at 21° C.

The '834 patent has previously been litigated before this Court in connection with the *Allergan, Inc. v. Alcon Inc.* action in the District of Delaware (C.A. No. 04-968 (GMS)). On July 26, 2005, this Court construed the term "about" in claims 1, 3, 10, and 12 of the '834 patent as "approximately." *Allergan Inc. v. Alcon Inc.*, C.A. No. 04-968 (GMS) (D. Del. July 26, 2005) (D.I. 109) (order construing certain terms of U.S. Patent Nos. 6,673,337 and 6,641,834). Alcon further filed a motion for summary judgment that, among other things, the '834 patent failed to satisfy the written description requirement of 35 U.S.C. § 112. *Allergan, Inc. v. Alcon Inc.*, C.A.

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[1] The "Exela Defendants" refer to Exela PharmSci, Inc., Exela Pharm Sci, Pvt. Ltd., Paddock Laboratories, Inc., and PharmaForce, Inc.

[2] Allergan is asserting claims 1-4, 6, 8-13, and 17-21 of the '834 patent. In reliance on Allergan's representation that it is asserting only those claims, the Exela Defendants are not addressing other claims or other patents, and Allergan is precluded from raising any of those claims or patents against the Exela Defendants. The Exela Defendants reserve the right to address the non-asserted claims of the '834 patent or any claim from the non-asserted patents (U.S. Patent Nos. 5,424,078, 6,562,873, 6,627,210, and 6,673,337) in the event that Allergan changes its position and attempts to assert them.

No. 04-968, 2005 U.S. Dist. LEXIS 32436, at *17 (D. Del. Dec. 8, 2005). On that issue, the Court ruled that a genuine issue of material fact existed with respect to whether the specification discloses to one skilled in the art the meaning of the claim term "0.15% (w/v/)." *Id.* at *28. The parties later settled on the eve of trial.

The Exela Defendants raise positions before this Court that are different from the positions Alcon raised in its claim construction briefing concerning two important claim limitations: (1) "A therapeutically effective aqueous ophthalmic composition comprising: up to about 0.15% (w/v) of [brimonidine] tartrate," and (2) "the composition having a pH of about 7.0 or greater."

The Exela Defendants propose that the Court adopt the following constructions for the claim limitations it regards as in dispute:[3]

| Asserted Claim of the '834 Patent | Proposed Construction |
|---|---|
| **Claim 1** | |
| 1. A therapeutically effective aqueous ophthalmic composition comprising: up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, | A water-based formulation containing between 0% and about 0.15% (w/v) of brimonidine tartrate for ophthalmic administration that is demonstrated to provide a therapeutic benefit to a patient to whom the formulation is administered. |
| | |
| the composition having a pH of about 7.0 or greater, | The therapeutically effective formulation referred to above has a pH of 7.0 or greater within measurement tolerances. In no event can the claim cover a formulation having a pH of 6.8 or below. |
| | |
| **Claim 10** | |

[3] In an effort to narrow the number of claims requiring construction before the Court, the Exela Defendants have reached agreement on the construction of the other claims or claim limitations of the '834 patent not specifically addressed in the Exela Defendants' opening claim construction brief. *See* Revised Joint Claim Charts (D.I. 46.) The Exela Defendants assert that any agreed-upon constructions do not inform or in any way create admissions regarding the claim limitations the Exela Defendants regard as in dispute.

| Asserted Claim of the '834 Patent | Proposed Construction |
|---|---|
| 10. A therapeutically effective aqueous ophthalmic composition comprising: up to about 0.15% (w/v) of a component selected from the group consisting of 5-bromo- 6-(2-imidozolin-2-ylamino) quinoxaline, salts of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, esters of 5- bromo-6-(2-imidozolin-2-ylamino) quinoxaline and mixtures thereof, | A water-based formulation containing between 0% and about 0.15% (w/v) of a component selected from the group consisting of: brimonidine; salts of brimonidine; esters of brimonidine; or mixtures thereof, for ophthalmic administration that is demonstrated to provide a therapeutic benefit to a patient to whom the formulation is administered. |
| | |
| the composition having a pH of about 7.0 or greater, | The therapeutically effective formulation referred to in claim 10 having a pH of 7.0 or greater within measurement tolerances. In no event can the claim cover a formulation having a pH of 6.8 or below. |

## II. NATURE AND STAGE OF THE PROCEEDING

This action is based on Exela's submission to the FDA of ANDA No. 78-590, which seeks approval to market 0.15% brimonidine tartrate ophthalmic solution, an anti-glaucoma drug. Allergan markets 0.15% brimonidine tartrate ophthalmic solution under the tradename Alphagan® P. At issue in this case is whether the product described in the Exela's ANDA would, if marketed, infringe the '834 patent and whether the '834 patent is valid.

This case is currently in fact discovery. A *Markman* hearing has been scheduled for July 16, 2008.

## III. SUMMARY OF ARGUMENT

The Exela Defendants' proposed claim constructions are based on the unambiguous language of the claims, the specification, and the prosecution history of the '834 patent.

First, the Exela Defendants contend that the first element of claims 1 and 10— "A therapeutically effective aqueous ophthalmic composition comprising: up to about 0.15% (w/v) of [brimonidine] tartrate (and/or its salts, esters, or mixtures thereof)"—be construed according

to its straightforward, ordinary meaning. This element requires a water-based ophthalmic formulation containing up to about 0.15% (w/v) of brimonidine tartrate that is demonstrated to provide a therapeutic benefit to a patient to whom the formulation is administered.

The Exela Defendants contend that the second element of claims 1 and 10—"the composition having a pH of about 7.0 or greater"—be construed to account for the unmistakable representations Allergan made to the Patent Office to obtain allowance of the patent. The intrinsic evidence makes clear two things: (1) the brimonidine tartrate composition must be formulated at a neutral pH (7.0) or greater (i.e. an alkaline pH); and (2) Allergan clearly and unmistakably disclaimed from the scope of its invention the pH range disclosed by the prior art ("about 6.6 to 6.8") in order to overcome an Office Action:

> The present invention is the result of the ***surprising finding*** that increasing the pH of a brimonidine solution to ***a pH of greater than about 7.0*** leads to similar efficacy at a 25% lower concentration (from 0.2% (w/v) to about 0.15% (w/v) or less) ***than is seen in a brimonidine solution at a pH of about 6.6-6.8***.

As set forth in detail below, the plain language of the claims of the '834 patent, its written description, and its prosecution history, informed by and consistent with the knowledge of the person of ordinary skill in the art, compel the constructions proposed by the Exela Defendants.

## IV. STATEMENT OF FACTS

The '834 patent was filed as a continuation application of Application Serial No. 10/236,656, which further claims priority back to Application Serial No. 09/904,018. Application Serial No. 09/904,018 has a priority date of July 14, 2000.

In 1996—several years before the earliest application leading to the '834 patent was filed—Allergan received approval from the FDA to market brimonidine tartrate and began selling the drug under the trade name Alphagan®. *See Allergan, Inc.*, 2005 U.S. Dist. LEXIS 32436, at *7. Alphagan® contained 0.2% (w/v) of brimonidine tartrate, and was formulated at

an acidic pH range. *See Id.* at *7-8. Compositions containing brimonidine tartrate are used to treat elevated pressure of the fluid in the eye, known as intraocular pressure.

In 2001, Allergan gained FDA approval to market an allegedly new formulation of the original Alphagan® product, Alphagan® P, which contained 0.15% of brimonidine tartrate, a 25% reduction in concentration over the original Alphagan® product. The pH of the brimonidine tartrate composition increased, from an acidic pH (pH of less than 7.0), to a pH of 7.0 or greater.

The basis for Allergan's '834 patent was the alleged similar efficacy of a 25% lower concentration of active ingredient, formulated in a composition at a higher pH (i.e., a pH of 7.0 or greater). As this Court previously observed, "the claimed compositions enhance the effectiveness of brimonidine tartrate (and other alpha-2-adrenergic agonist components) by increasing its apparent water solubility at pHs higher than neutral, or 7.0." *Allergan, Inc.*, 2005 U.S. Dist. LEXIS 32436, at *11.

The originally filed application of the '834 patent had two claims specifying pH. One referred to "a pH of about 7 or greater" and the other to "a pH of about 7 to about 9."[4] In a Preliminary Amendment, Allergan amended the claims to add a decimal place, claiming the more precise pH of "about 7.0 or greater."[5]

In the first Office Action, the Examiner rejected the claims as obvious over the prior art.[6] In its written reply to the Office Action, Allergan noted that the prior art 0.2% brimonidine

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[4] Prosecution history of U.S. Patent No. 6,641,834, Application as filed September 6, 2002, at 36 (Tab 6.) All references to the prosecution history in the Exela Defendants' opening claim construction brief refer to the prosecution history of the '834 patent.

[5] Preliminary Amendment dated September 6, 2002, at 1-3 (Tab 6).

[6] Office Action mailed December 18, 2002, at 4-5 (Tab 6).

solution (Alphagan®) was formulated at an acidic pH.[7] Allergan also argued, in an attempt to distinguish the prior art, that:

> The present invention is the result of the ***surprising finding*** that increasing the pH of a brimonidine solution to ***a pH of greater than about 7.0*** leads to similar efficacy at a 25% lower concentration (from 0.2% (w/v) to about 0.15% (w/v) or less) ***than is seen in a brimonidine solution at a pH of about 6.6-6.8***.[8]

Allergan also filed a declaration from one of its employees that allegedly showed that the efficacy of the prior-art 0.2% brimonidine tartrate composition at an acidic pH was similar to the 0.15% brimonidine composition at pH 7.2 in lowering intraocular pressure.[9]

After requiring a further limitation of "about 21° C" to be added, the Examiner allowed the claims.

## V. ARGUMENT

### A. Claim Construction Principles

Because patent claims define the invention and delimit a patentee's right to exclude, a district court construes patent claims as a matter of law to determine their meaning and scope. *Markman v. Westview Instrs., Inc.*, 52 F.3d 967, 976, 980 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996).

A district court should construe claim language to discern the meaning it would have to a person of ordinary skill in the art at the time of the invention. *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004). Guidance as to the meaning of claim language comes from two sources: intrinsic evidence and extrinsic evidence.[10] *Vitronics*

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[7] Reply to Office Action mailed March 17, 2003, at 4 (Tab 6).

[8] *Id.*

[9] *Id.*

[10] The Federal Circuit case *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), provides an in-depth commentary of claim construction principles. *Phillips* noted that there is no "magic

*Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1581-83 (Fed. Cir. 1996). The intrinsic evidence consists of the patent and its prosecution history. *Id.* at 1582. Extrinsic evidence is all evidence external to the patent and its prosecution history, such as dictionaries, treatises, inventor testimony, and expert testimony. *Markman*, 52 F.3d at 980.

A patent's claims define the invention and the patentee's right to exclude. *Innova*, 381 F.3d at 1115. Accordingly, a district court should look to the words of the claims themselves to ascertain the scope of the patented invention. *Vitronics*, 90 F.3d at 1582.

Claim construction also requires examination of the patent's written description and prosecution history. *Markman*, 52 F.3d at 979-80. The court has "broad power to look as a matter of law to the prosecution history of the patent in order to ascertain the true meaning of language used in the patent claims." *Id.*

In particular—and important to the Court's construction of certain claim limitations in this case—a court may construe, and limit the scope of, the claims according to the doctrine of prosecution disclaimer. Specifically, "'a patentee may limit the meaning of a claim term by making a clear and unmistakable disavowal of scope during prosecution.'" *See Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1374 (Fed. Cir. 2008) (holding that "the sum of the patentees' statements during prosecution would lead a competitor to believe that the patentee had disavowed coverage of laptops") (citing *Purdue Pharma L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006)). A patentee could do so, for example, by clearly

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formula" for conducting claim construction and instead identified a hierarchy for using intrinsic and extrinsic evidence to discern the meaning of claim language. 415 F.3d at 1324. It said that "the claims themselves provide substantial guidance . . . ." *Id.* at 1314. It then stated that a court may "rely heavily on the written description for guidance as to the meaning of the claims." *Id.* at 1317. It also indicated that the prosecution history may be also be consulted claim-construction purposes. *Id.* It then explained that extrinsic evidence is "less significant than the intrinsic record for determining 'the legally operative meaning of claim language.'" *Id.* (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

characterizing the invention in a way to try to overcome rejections based on prior art. *Id*; *see, e.g., Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349 (Fed. Cir. 2004) (limiting the term "transmitting" to require direct transmission over telephone line because the patentee stated during prosecution that the invention transmits over a standard telephone line, thus disclaiming transmission over a packet-switched network); *Alloc, Inc. v. ITC*, 342 F.3d 1361, 1372 (Fed. Cir. 2003) (finding the patentee expressly disavowed floor paneling systems without "play" because the applicant cited the feature during prosecution to overcome prior art); *Bell Atl. Network Servs. v. Covad Commc'ns Group, Inc.*, 262 F.3d 1258, 1273 (Fed. Cir. 2001) (limiting operation of the "transceiver" to the three stated modes because of clearly limiting statements made by the patentee to try to overcome a prior art rejection).

Lastly, a district court may consider extrinsic evidence to assist it in understanding scientific principles and the technology at the time of the invention. *See Markman*, 52 F.3d at 980. And a court may employ extrinsic evidence for claim-construction purposes. *Phillips*, 415 F.3d at 1317. But a court should not use extrinsic evidence to vary or contradict the meaning of claim language where the intrinsic evidence determines the meaning. *Vitronics*, 90 F.3d at 1583-85.

### B. The First Element of Claims 1 and 10 — "A Therapeutically Effective Aqueous Ophthalmic Composition Comprising: Up to About 0.15% of [Brimonidine] Tartrate (or its Salts, Esters, or Mixtures Thereof)"— Should Be Construed According to its Plain Meaning as Confirmed by the Intrinsic Evidence

Each claim of the '834 patent requires a "therapeutically effective" composition containing concentrations of up to about 0.15% brimonidine tartrate, the active ingredient. Claim 1 is representative, and reads:

> 1. A therapeutically effective aqueous ophthalmic composition comprising: up to about 0.15% (w/v) of [brimonidine] tartrate,
>
> the composition having a pH of about 7.0 or greater,
>
> and the [brimonidine] tartrate being soluble in the composition at about 21 °C.

Claim 10 mirrors the language of claim 1 but also recites the salts, esters, and mixtures of brimonidine tartrate. The Court should adopt the Exela Defendants' proposed construction of the entire first element of claims 1 and 10: "[a] therapeutically effective aqueous ophthalmic composition comprising: up to about 0.15% (w/v) of [brimonidine] tartrate (or its salts, esters, and mixtures thereof)." The Exela Defendants propose that this element, as whole, be construed as: **a water-based formulation containing between 0% and about 0.15% (w/v) of brimonidine tartrate (or its salts, esters, or mixtures thereof) for ophthalmic administration that is demonstrated to provide a therapeutic benefit to a patient to whom the formulation is administered**.

First, there is no dispute that the phrase "aqueous ophthalmic composition," as used in claims 1 and 10, should be construed according to its plain and ordinary meaning, in this case "a water-based formulation." Example 1 of the '834 patent discloses that the "formulation vehicle," into which the "ingredients of the Ophthalmic Solution" was dissolved in a "separate container with "purified water."[11] The compositions of the ophthalmic compositions described in Example 1 are listed in Table 1, with "Purified Water" one of the ingredients of the composition.[12]

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[11] *See* U.S. Patent No. 6,641,834, Col. 13:24-40 (Tab 5). All patent citations in the Exela Defendants' opening claim construction brief refer to the '834 patent.

[12] Col. 14:5-15 (Tab 5).

Merriam-Webster's Medical Dictionary, moreover, defines "aqueous" as "made from, with, or by water (an ~ solution)."[13]

Next, the "aqueous ophthalmic composition" must be for "ophthalmic administration" (i.e., directly administered to the eye of a patient in need). The claims require ophthalmic administration because the "invention facilitates transport of [the active ingredient and excipients] across lipid membranes" (i.e., the membranes of the eye).[14]

The brimonidine tartrate formulations according to the '834 patent must further be demonstrated to provide a therapeutic benefit or effect. Claims 1 and 10 both define the invention as "[a] ***therapeutically effective*** aqueous ophthalmic composition."[15] The phrase "therapeutically effective" should be accorded its plain and ordinary meaning. *See Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 344 F.3d 1274, 1278 (Fed. Cir. 2003) (construing "effective amount" to have its ordinary meaning because the patentee did not define it differently). And the '834 patent specification repeatedly emphasizes the criticality that the brimonidine composition must be "therapeutically effective."[16]

Similarly, the prosecution history explicitly teaches that that the claimed brimonidine formulation must demonstrate a therapeutic benefit. The claims of the application that led to the '834 patent were added by a Preliminary Amendment.[17] It was in these new claims that the 0.15% limitation appeared for the first time.

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[13] Merriam-Webster's Medical Dictionary 52, 1996 (Tab 15).

[14] Col. 1:64-67 (Tab 5).

[15] Col. 16:45-51; Col. 17:7-16 (Tab 5).

[16] Col. 1:15-19; Col. 4:12-15 (Tab 5).

[17] Preliminary Amendment dated September 6, 2002, at 1-3 (Tab 6).

Immediately after Allergan introduced the 0.15% limitation into the claims,[18] the Examiner rejected all of the claims as obvious.[19] In a written response mailed March 17, 2003, Allergan amended the claims and argued that the claimed invention was supported by "unexpected results."[20] Allergan also amended the claims to require that the claimed compositions be demonstrated to be "therapeutically effective."[21] In that response, Allergan reiterated its position that "therapeutically effective" compositions with brimonidine at concentrations of about 0.15% or less would have been "surprising:"[22]

> Thus, the present invention is drawn to surprising new ***therapeutic compositions*** comprising at least a 25% lower concentration of brimonidine than previous ophthalmic formulations . . .

(emphasis added). Allergan, again, emphasized that the claimed brimonidine compositions must have a therapeutic benefit.

The Exela Defendants' proposed construction —**a water-based formulation containing between 0% and about 0.15% (w/v) of brimonidine tartrate (or its salts, esters, or mixtures thereof) for ophthalmic administration that is demonstrated to provide a therapeutic benefit to a patient to whom the formulation is administered**—is consistent with the claims, specification, prosecution history, and the plain and ordinary meaning of the phrase.

### C. The Claim Limitation "The Composition Having a pH of About 7.0 or Greater"

The Exela Defendants propose the following construction for the "the composition having a pH of about 7.0 or greater" elements of claims 1 and 10:

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[18] *Id.*

[19] Office Action mailed December 18, 2002, at 4 (Tab 6).

[20] Reply to Office Action mailed March 17, 2003, at 3-5 (Tab 6).

[21] *Id.* at 2.

[22] *Id.* at 5 (emphasis added).

| Asserted Claims of the '834 Patent | Proposed Construction |
|---|---|
| **Claims 1 and 10** | |
| the composition having a pH of about 7.0 or greater, | The therapeutically effective formulation referred to above has a pH of 7.0 or greater within measurement tolerances. In no event can the claim cover a formulation having a pH of 6.8 or below. |

As noted above, the Court previously construed the word "about" in claims 1, 3, 10, and 12 in the '834 patent. There, the Court construed "about" as "approximately." *Allergan Inc. v. Alcon Inc.*, No. 04-968 (GMS) (D. Del. July 26, 2005) (construing certain terms of U.S. Patent Nos. 6,673,337 and 6,641,834).

The Exela Defendants' proposed construction of the element "the composition having a pH of about 7.0 or greater" is consistent with the Court's previous construction of the term "about" within this claim element, but adds specificity based on a prosecution history disclaimer position that Alcon did not assert in the earlier litigation. While Alcon referenced Allergan's prosecution history arguments in its briefing, Alcon did not seek a construction that specifically incorporated Allergan's disclaimer of pH values below 6.8.[23] Accordingly, the Exela Defendants believe that this issue has not been previously presented to the Court.

Moreover, although a court may defer to a previous construction at its discretion, the right of a new defendant to bring new arguments to the attention of the court, and fully litigate its claims, is particularly persuasive and militates against adopting a previous claim construction. *See Texas Instruments, Inc. v. Linear Tech. Corp.*, 182 F. Supp. 2d 580, 589 (E.D. Tex. 2002);

[23] Alcon argued for a construction that excluded pH values below 6.95. *See* Memorandum in Support of Alcon's Proposed Claim Construction, filed May 2, 2005 (C.A. No. 04-968-GMS) (D.I. 54).

*see also Inpro II Licensing, S.A.R.L. v. T-Mobile USA, Inc.*, 450 F.3d 1350, 1359 (Fed. Cir. 2006) (citing *Texas Instruments* in a concurring opinion for proposition that "the court may defer to a prior claim construction, though it is not necessarily bound by it").

**1. Any Degree of Numerical Uncertainty Created By the Term "About" Should Be Resolved By Construing the Claim to Cover Only pH Levels Within Minor Experimental Error Around an Exact pH of 7.0**

The intrinsic evidence in this case establishes that the claimed brimonidine tartrate formulations must be formulated at a neutral pH or greater. The Exela Defendants propose that the claim element "the composition having a pH of about 7.0 or greater" limitation may be understood as expressing a degree of observational measurement error. Variability (reflected in this case with the term "about") is an inherent part of things being measured and of the measurement process.

The Federal Circuit has recognized that a patentee may use the term "about" to avoid strict numerical boundaries when an exact limitation is inappropriate because of the subject matter. *See Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217-18 (Fed. Cir. 1995).

The scope of "about" depends on its context and the precision or significance of the measurements used. *See Pall*, 66 F.3d at 1217; *Modine Mfg. Co. v. U.S. Int'l Trade Comm'n.*, 75 F.3d 1545, 1554 (Fed. Cir. 1996). The Federal Circuit has approved of the use of experimental error (i.e., an estimation of the precision with which an experimental value can be determined) to interpret the range of values encompassed by the term "about." *See B.J. Services Co. v. Halliburton Energy Serv.*, 338 F.3d 1368, 1372-73 (Fed. Cir. 2003) (approving patentee's interpretation of "about" as encompassing the range of experimental error in response to an indefiniteness attack); *Hybritech Inc. v. Abbott Labs*, 849 F.2d 1446, 1455 (Fed. Cir. 1988) (finding no error in district court's construction of the scope of "at least about 108 liters/mole" claim limitation based on the amount of error inherent in such measurements).

Courts have refused to extend the scope of "about" unless the claims, specification, or prosecution history provided a basis to do so. *See Pall*, 66 F.3d at 1217. Here, there is no basis in the intrinsic evidence to expand the scope of "the composition having a pH of about 7.0 or greater"—covering a neutral or alkaline pH—to cover acidic pH levels, e.g., pH levels less than 7.0. The Court should therefore construe the entire claim limitation "the composition having a pH of about 7.0 or greater" as **the therapeutically effective formulation of the claim has a pH of 7.0 or greater within measurement tolerances**. In no event can the claimed composition have a pH of 6.8 or below because of the prosecution disclaimer set forth below.

**a. pH is a Measurement of the Acidity or Alkalinity of an Aqueous Solution and Small Differences in pH Reflect Differences on an Order of Magnitude**

pH is a measure of the alkalinity or acidity of a solution.[24] Solutions with pH values less than 7.0 are "acidic," and those with pH values greater than 7.0 are "alkaline" (or "basic"). Solutions with a pH of 7.0 are neutral (i.e., neither acidic nor alkaline).[25] An ordinarily skilled artisan would also understand that, because the pH scale is logarithmic, differences in single whole numbers of values (e.g., between pH 7.0 and pH 6.0) actually reflect differences of an entire order or magnitude—differences in concentration larger than the values themselves seem to indicate.[26]

**b. Claims 1 and 10 Recite the pH of the Claimed Composition to the Tenth of a Unit**

The pH of the therapeutically effective formulation referred to in claims 1 and 10 is expressed to the ***tenth of a unit***, and not whole pH levels (e.g., a pH of 6). Thus, an ordinary skilled artisan would immediately recognize the importance of maintaining a pH of the aqueous

[24] Hawleys Condensed Chemical Dictionary, 853-54 (2001) (Tab 16).
[25] *Id.*
[26] *Id.*

ophthalmic solution as close to a neutral pH of 7.0 (or greater than 7.0) as possible, because of the substantial differences in magnitude between two different pHs that are numerically close (e.g., 6.9 vs. 7.0). Indeed, the '834 patent specification emphasizes the large differences between varying pH levels: "the solubility of Brimonidine tartrate is highly pH-dependent and spans ***more than two orders of magnitude over the pH range of 5-8***."[27]

**c. The Specification and Prosecution History Emphasize the Importance of Formulating the Brimonidine Tartrate Formulation at a Neutral or Alkaline pH**

The '834 patent specification further demonstrates that the claimed compositions must be formulated at a neutral pH (7.0) or greater. The specification identifies the claimed invention as compositions containing alpha-2-adrenergic agents (e.g., brimonidine tartrate as an active ingredient) with "components" effective in enhancing the effectiveness of such agents by increasing their solubility at pHs higher than neutral (i.e., greater than 7.0).[28] Such compositions are formulated in such a manner to be better able to cross the "lipid membranes" (e.g., a biologic cellular barrier) of the eye in order to provide a therapeutic benefit.[29]

The specification repeatedly confirms the importance of maintaining the claimed compositions at a neutral pH or greater. At ***no point*** in the specification does Allergan indicate that the claimed composition can exist at an acidic pH level, e.g., with a pH of less than 7.0.

For example, the specification says the following about the pH levels of the claimed brimonidine formulation:

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[27] Col 14:18-21 (Tab 5).

[28] Col. 2:9-20 (Tab 5).

[29] Col. 4:33-38 (Tab 5).

- In one embodiment, the alpha-2-adrenergic components in the claimed compositions are "more soluble in neutral [e.g., 7.0], preferably alkaline [e.g., greater than 7.0] biological environments."[30]
- "Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's ***greater than*** *7*."[31]
- "Brimonidine tartrate, are amine containing and preferably have pKa's of ***greater than*** *7*, preferably about 7.5 to 9."[32]

Indeed, this Court has recognized that the '834 patent specification teaches that "the claimed compositions enhance the effectiveness of brimonidine tartrate (and other alpha-2-adrenergic agonist components) by increasing its apparent water solubility ***at pHs higher than neutral, or 7.0***." *Allergan, Inc.*, 2005 U.S. Dist. LEXIS 32436, at *11 (emphasis added).

The prosecution history confirms that Allergan restricted the pH range of the brimonidine tartrate formulation to a neutral pH or greater. The originally filed application had two claims specifying pH. One referred to "a pH of about 7 or greater" and the other to "a pH of about 7 to about 9."[33] But the applicants requested examination of a more precise pH. Specifically, Allergan amended its claims to limit them to a more precise pH of "about 7.0 or greater."[34] Thus, Allergan narrowed the claims from a whole number ("a pH of about 7 or greater") to claim a more precise pH in terms of tenths of that number ("a pH of about 7.0 or greater").

Accordingly, any ambiguity in the claim caused by the presence of the term "about" should be limited to expressing a degree of measurement error around an exact pH of 7.0.

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[30] Col. 2:20-25 (Tab 5).
[31] Col. 4:22-26 (emphasis added) (Tab 5).
[32] Col. 5:65-67 (emphasis added) (Tab 5).
[33] Application as filed September 6, 2002, at 36 (Tab 6).
[34] Preliminary Amendment dated September 6, 2002, at 1-3 (Tab 6).

### 2. In No Event Can the Limitation Cover Any Brimonidine Formulation with the pH Level—6.6 to 6.8—Disclaimed by the Patentee During Prosecution

During prosecution, Allergan unambiguously disclaimed from the scope of the asserted claims **formulations having a pH of 6.8 or below**.

In the first Office Action of the application that lead to the '834 patent, the Examiner rejected the claims as obvious over the prior-art Burke patent.[35] The Examiner recognized that the Burke patent disclosed the claims' elements (except the chloride component) and that an ordinarily skilled artisan could determine the most efficacious dose by carrying out a dose response curve.[36]

In its written reply to the Office Action, in an effort to distinguish the prior art compositions, Allergan argued that:

> The present invention is the result of the ***surprising finding*** that increasing the pH of a brimonidine solution to ***a pH of greater than about 7.0*** leads to similar efficacy at a 25% lower concentration (from 0.2% (w/v) to about 0.15% (w/v) or less) ***than is seen in a brimonidine solution at a pH of about 6.6-6.8***.[37]

In this argument, Allergan specifically and directly contrasted "a pH of greater than about 7.0" with "a pH of about 6.6-6.8"—making perfectly clear that the former does not include the latter. In so doing, Allergan unambiguously and unmistakably disclaimed any range of pH from "about 6.6-6.8."

In conclusion, the Court should adopt the Exela Defendants' proposed construction for the claim limitation "the composition having a pH of about 7.0 or greater": **The therapeutically**

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[35] Office Action mailed December 18, 2002, at 4 (Tab 6).

[36] *Id*

[37] Reply to Office Action mailed March 17, 2003, at 4 (Tab 6).

**effective formulation of the claim has a pH of 7.0 or greater within measurement tolerances. In no event can the claim cover a formulation having a pH of 6.8 or below.**

## VI. CONCLUSION

The Exela Defendants' proposed constructions are based on the intrinsic record as understood by one of ordinary skill in the art. For the foregoing reasons, the Exela Defendants respectfully request that the Court enter an order construing the claim limitations of the '834 patent as proposed by the Exela Defendants.

Kelly E. Farnan

Frederick L. Cottrell III (#2555)
Kelly E. Farnan (#4395)
Richards, Layton & Finger
One Rodney Square
920 North King Street
P.O. Box 551
Wilmington, Delaware 19801
Tel.: (302) 651-7700
Fax: (302) 651-7701
cottrell@rlf.com
farnan@rlf.com

*Attorneys for Defendants Exela PharmSci, Inc. Exela Pharm Sci, Pvt. Ltd., Paddock Laboratories, Inc., and PharmaForce, Inc.*

Of Counsel:

Daniel G. Brown
Arthur L. Hoag
Barry S. White
David A. Zwally
Omar Jabri
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, New York 10151
Tel.: (212) 588-0800
Fax: (212) 588-0500

Dated: June 3, 2008

**UNITED STATES DISTRICT COURT**
**DISTRICT OF DELAWARE**

**CERTIFICATE OF SERVICE**

I HEREBY CERTIFY that on June 3, 2008, I electronically filed the foregoing with the Clerk of Court using CM/ECF and caused the same to be served on the plaintiff at the addresses and in the manner indicated below:

**E-MAIL AND HAND DELIVERY**

William J. Marsden, Jr.
Fish & Richardson, P.C.
919 N. Market Street, Suite 1100
Wilmington, Delaware 19899-1114

Richard L. Horwitz
Potter, Anderson & Corroon, LLP
1313 N. Market Street
Hercules Plaza
Wilmington, Delaware 19899-0951

I further certify that on June 3, 2008, the foregoing document was sent to the following non-registered participants in the manner indicated:

**E-MAIL**

Juanita R. Brooks
Fish & Richardson
12390 El Camino Real
San Diego, CA 92130-2081

Robert B. Breisblatt
Katten Muchin Rosenmann LLP
525 West Monroe Street
Chicago, IL 60601-3693

William C. Shear
Fish & Richardson
1717 Main Street, Suite 5000
Dallas, TX 75201

Jonathan E. Singer
Michael J. Kane
Fish & Richardson
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402

Kelly E. Farnan (#4395)